1,10-Diaza-4,7,13,16-tetraoxacyclooctadecane-1,10-bis(malonate), a Ligand with High Sr^{2+}/Ca^{2+} and Pb^{2+}/Zn^{2+} Selectivities in Aqueous Solution

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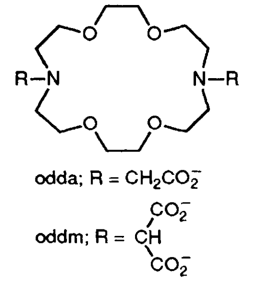
The stability constants of the complexes of 1,10-diaza-4,7,13,16-tetraoxacyclooctadecane-1,10-bis(malonate) formed with alkaline-earths, lanthanides, zinc, cadmium and lead are larger for larger metal ions, which is manifested in unusually high Sr^{2+}/Ca^{2+} and Pb^{2+}/Zn^{2+} selectivities in aqueous solution.

The aza-crown ligand 1,10-diaza-4,7,13,16-tetraoxacyclooctadecane (18-aneN_2O_4) exhibits a remarkable selectivity towards large metal ions, but the stability constants of the complexes are relatively low in aqueous solution.[1,2] Complex stabilities can be increased by the attachment of ionizable functional groups (*e.g.* acetate) to the nitrogen atoms but, in general, this modification leads to a decrease in selectivity. In spite of the loss of selectivity, complexation properties of the functionalized derivatives of 18-aneN_2O_4 differ considerably from those of the acyclic polyamino-polycarboxylates, such as ethylenediaminetetraacetic acid (edta). The equilibrium and kinetic properties of the complexes formed with 18-aneN_2O_4-*N*,*N*′-diacetate (odda^{2-}) have been studied in detail.[3–7] The stability constants of the lanthanide (Ln^{3+}) complexes of odda decrease with the rise of the atomic number,[4] which is very unusual. The high selectivity of odda, observed for Pb^{2+} over Zn^{2+},[4,6] seems to be promising in the development of new chelating agents which are needed in the therapy of lead poisoning.[8]

It is also known that acyclic polyamino-polycarboxylates are not effective in mobilizing the radioactive isotopes of Sr from the body, since the complexes of the Ca^{2+} ion, of smaller size, are more stable than the complexes of Sr^{2+}. However, the stability constants of Ca(odda) and Sr(odda) are equal,[3,4] which indicates the potential usefulness of the derivatives of 18-aneN_2O_4 in efforts aimed at synthesizing ligands, exhibiting selectivity for Sr^{2+} over Ca^{2+}.

Recently we have prepared several new derivatives of



odda; R = $CH_2CO_2^-$

oddm; R = $CH(CO_2^-)_2$

18-aneN$_2$O$_4$, and the ligand 18-aneN$_2$O$_4$-*N*,*N*′-bis(malonate) (oddm^{4-}) exhibited very interesting complexation properties as it proved to be highly selective for the large size metal ions.

The ligand oddm was synthesized by the reaction of 1,10-diaza-4,7,13,16-tetraoxacyclooctadecane and disodium bromomalonate in an aqueous solution at *ca.* pH 10. The reaction mixture was evaporated and the tetrasodium salt of the 18-aneN$_2$O$_4$-*N*,*N*′-bis(malonate) and sodium bromide were extracted together from the solid residue by absolute ethanol. The solvent was evaporated again, and NaBr was extracted from the remaining solid with an ethanol–water mixture, when the ligand was obtained as a pure tetrasodium salt, Na$_4$oddm. The yield is 90%. The purity of the product (99.5% at least) was controlled by ^{1}H NMR spectroscopy at different pHs. The amount of the N-bound malonate was determined (calc. 36.45, found 36.08%) by a decarboxylation reaction in acidic solution.

The protonation constants of the ligand and the stability constants of the complexes were determined by pH-potentiometric titration at 25 °C in 0.15 mol dm^{-3} NaCl. The H$^+$ ion concentration was obtained from the pH data by a known method.[9] During the preparation of the samples for the titration, diluted HCl was slowly added to the stirred solution of Na$_4$oddm, since at lower pHs (pH <2) a decarboxylation reaction occurs.[10]

Comparison of the data clearly indicates that the trend in the log*K* values of the complexes formed with oddm is quite unexpected. The stability constants of the alkaline-earths increase in order Mg $<$ Ca $<$ Sr $\approx$ Ba, which is very unusual, similarly to the much higher log*K* value of Ce(oddm)$^-$, as compared to the log*K* value of Lu(oddm)$^-$. The selectivity for Pb^{2+} over Zn^{2+} is higher than in the case of the complexes of odda. The log*K* value of Mn(oddm)$^{2-}$ is higher than that of the Zn(oddm)$^{2-}$, which is also not regular. All these results demonstrate that the ligand oddm is highly selective for the large size metal ions.

Since the stability constant of the complex Sr(oddm)$^{2-}$ is larger than that of Ca(oddm)$^{2-}$, the ligand oddm appears to be promising in mobilizing freshly incorporated radioactive Sr. Animal experiments have shown that intravenously injected Na$_2$[Ca(oddm)] significantly increases the rate of decorporation, and reduces the whole-body retention of the ^{85}Sr isotope below 5–10% of the initial body burden.[12]

The structure of the complexes of oddm in solution is probably similar to that of the complexes of odda.[4,13] The four oxygen atoms of 18-aneN$_2$O$_4$ are coordinated to the metal ion approximately in a plane, and one of the malonate groups is coordinated above this plane, while the other one below the plane.

In the ^{1}H NMR spectrum of the free ligand (pH 11) the N–CH$_2$ and O–CH$_2$ protons give triplet signals (δ 2.89 and 3.63), while the O–CH$_2$–CH$_2$–O protons result in a singlet (δ 3.68). In the complexes the O–CH$_2$ and O–CH$_2$–CH$_2$–O protons appear as broad, overlapping multiplets, but the signal of the N–CH$_2$ protons is well-separated and gives some information on the rigidity of the coordinated macrocycle, which strongly depends on the size of the metal ion. Small size metal ions, such as Mg^{2+}, Zn^{2+} and Lu^{2+} result in a broadening of the signal of the N–CH$_2$ protons. For the complex Ca(oddm)$^{2-}$ two broad, equal-intensity resonances appear at 25 °C, which coalesce at about 50 °C and narrow with rising temperature. These two resonances are strongly split for the complexes of the larger size Sr^{2+}, Ba^{2+} and La^{3+}, which indicates the long life-time of both the M–N and M–O bonds,[14] and thus the rigid structure of the complexes. (The N–CH$_2$–CH$_2$–O ethylene protons constitute an AA′XX′ splitting system, and the signals observed separately, form a part of this splitting pattern).

The high selectivity observed for the large size metal ions cannot be explained exclusively by their higher 'size-match' selectivity. Larger metal ions can coordinate more carboxylate oxygens on average owing to their higher coordination number (the life-time of metal–oxygen bonds is very short). The interaction with more donor atoms may result in larger stability constants, and lead to the higher selectivity for the large metal ions over the smaller ones.

Table 1 Protonation constants (log*K*$_i$) of the ligands odda, oddm and edta and the stability constants (log*K*) of the complexes

	odda[a]	oddm[b]	edta[c]
logK_1	8.45	7.95	10.17
logK_2	7.80	7.35	6.11
logK_3	2.90	3.03	2.68
Mg^{2+}	—	2.53	8.83
Ca^{2+}	8.39	7.54	10.61
Sr^{2+}	8.29	9.79	8.68
Ba^{2+}	7.63	9.76	7.80
Mn^{2+}	—	7.40	13.81
Zn^{2+}	8.42	6.28	16.44
Cd^{2+}	11.07	10.27	16.36
Pb^{2+}	13.55	13.03	17.88
Ce^{3+}	12.23	16.15	15.94
Lu^{3+}	10.84	10.74	19.80

[a] Ref. 4, 0.10 mol dm^{-3} KCl, 25 °C. [b] This work, 0.16 mol dm^{-3} NaCl, 25 °C. [c] Ref. 15, 0.10 mol dm^{-3} KCl, 25 °C.

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